Role of veterinary therapeutics in bacterial resistance development: animal and public health perspectives

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The American Academy of Veterinary Pharmacology and Therapeutics recently conducted a special symposium held in College Park, Md, on January 19 to 21, 1998. The title of the symposium was "The role of veterinary therapeutics in bacterial resistance development: animal and public health perspectives." The symposium was cosponsored by the AVMA, the Center for Veterinary Medicine of the FDA (FDA-CVM), and the Center for Government and Corporate Veterinary Medicine, Virginia-Maryland Regional College of Veterinary Medicine. A task force was convened and charged with summarizing information presented, identifying gaps in knowledge and research needs, and delineating what constitutes prudent use of antimicrobials in food animals. Recommendations, specific to the veterinary community (including, but not limited to, veterinarians and producers, the pharmaceutical industry, and regulatory agencies) are broad enough to encompass practices affecting all public and private health officials in human and animal medicine, and are to be considered guidelines for expansion into complete initiatives.

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Preamble
The purpose of this symposium was to bring together representatives of the livestock and poultry industries, the veterinary profession, government agencies, and pharmaceutical companies. In addition, it was intended to provide a public forum for balanced scientific discussion on the role of veterinary therapeutics in the emergence of bacterial resistance, and to provide a mechanism for recommending future action.

Continued use of antimicrobials (as well as other possible selective factors; eg, use of disinfectants and bacterial vaccines) can lead to the selection of resistant populations of bacteria. This selection can lead to reduced effectiveness of existing antimicrobial agents used in the treatment and control of bacterial diseases. Antimicrobial use in food animals may contribute to shifts in the minimum inhibitory concentrations (MIC) of some antimicrobials for zoonotic organisms. The clinical importance of MIC shifts attributable to veterinary antimicrobial use in nonhuman animals, compared with those shifts attributable to human antimicrobial use in human beings, on the therapeutic efficacy of antimicrobials in human medicine remains to be quantified. This is likely to be dependent on the extent of MIC shifts, the drug, and the therapeutic indication for which the drug is used. However, it is clear that antimicrobials are vital for the effective practice of human and veterinary medicine. Therefore, we need to foster the use of antimicrobials in a manner that promotes their effectiveness in the animal and human populations and minimizes their impact on bacterial resistance. Rational, prudent antimicrobial use in animals must now include considerations that address the impact of antimicrobial use on resistance emergence as well as the long-standing considerations of target animal efficacy, target animal safety, drug residues in food, and environmental safety.

Scope of Meeting
The focus of the meeting was on the therapeutic use of antimicrobials in food-producing animals, as defined by the FDA-CVM to mean the treatment, control, and prevention of bacterial disease. The subtherapeutic use of antimicrobials (ie, use for growth promotion) was not...
addressed. However, this by no means minimizes the importance of addressing subtherapeutic use, and the task force urges appropriate stakeholders to address this topic in another conference, sponsored by an organization more closely linked to that use pattern.

Summary of the Meeting

Participation in the meeting was open to any interested party. One hundred sixty-two registrants and 27 speakers and moderators comprised the meeting attendance, with representation from the United States as well as 7 other countries. Organizations represented included animal-producer groups, veterinary practitioner and specialty associations, veterinary pharmacology, veterinary microbiology, public-health and consumer-interest groups, and members from congressional committees. United States government agencies represented included the FDA-CVM, the USDA, the Centers for Disease Control and Prevention (CDC), and the General Accounting Office.

The meeting consisted of several presentations each day, interspersed with considerable discussion time. Several presentations focused on the cellular and molecular mechanisms for the development and transfer of antimicrobial resistance. The tools now available for conducting molecular epidemiologic investigations regarding the development and spread of resistant bacterial populations among animals and human beings were also discussed. Other presentations described the current on-farm husbandry and health-maintenance practices for beef cattle, dairy cattle, swine, and poultry. Food safety issues were highlighted, including an overview of the President’s Food Safety Initiative, the USDA Hazard Analysis and Critical Control Point approach to improving food safety at the slaughterhouse and food processor levels, and the education of consumers to increase awareness of food safety measures at home. Included were discussions of how the selection of antimicrobial resistant populations of bacteria relates to food safety. Speakers described the epidemiologic characteristics of salmonellosis in human beings and animals, and a representative from the CDC drew a link between the 2 on the basis of epidemiologic observations. Considerable discussion centered around the need, and the current capability, to assess the risk of development of antimicrobial resistance in human infections attributable to antimicrobial use in animals. Current antimicrobial resistance surveillance and monitoring technology, limitations, and of susceptibility profiles for food-borne pathogens were provided by several speakers. Finally, new antimicrobial drug discovery efforts and new compounds and classes of compounds that are nearing the marketplace for human medicine were highlighted. The historical relationship between new classes of antimicrobials for human use, and their ultimate use thereafter in veterinary medicine (and the lack of resources available to generate new antimicrobial classes solely for use in animals), were also reviewed.

Task Force Recommendations

The therapeutic use of antimicrobials in animals is needed to relieve pain and suffering in livestock. Therapeutic use of antimicrobials may also minimize the shedding of zoonotic bacteria in the environment, and ultimately reduce the number of zoonotic bacteria in animals at slaughter. Furthermore, there is an impact on the development of antimicrobial resistance in zoonotic bacterial populations as a consequence of the use of antimicrobials in food animals. The extent of these impacts will vary with drug, delivery method, pharmacokinetics, pharmacodynamics, bacterial species, and other possible factors. However, the degree (or “attributable fraction”) to which therapeutic antimicrobial use in food animals contributes to the emergence of resistance in zoonotic food-borne pathogens in human beings has not been quantified. Furthermore, therapeutic use of antimicrobials in animals is believed to represent a small but real fraction of the overall selection for resistant human pathogens. Collectively, these observations should spur the active and rapid initiation of measures to direct the use of antimicrobials in animals in ways that not only ensure efficacy and safety to the target animal, and prevent unsafe drug residues from entering the human food chain, but also minimize the selection for resistant organisms.

Proper use needs to be tailored to the animal species and its husbandry, drug, bacterial infection, and its population dynamics. Rapid information retrieval in species-tailored formularies (US Pharmacopeia Drug Index veterinary monographs and algorithms for each food-animal species, including practitioner, management, microbiology, pharmacology, and food safety input) is a critical part of prudent use of antimicrobials.

Concerns about antimicrobial resistance are affecting the approval of new antimicrobial agents for use in food animals in the United States. Because of the current and potential value of fluoroquinolones in human and veterinary medicine, the exposure of bacterial populations to fluoroquinolones in any species should be reserved for applications where other available treatments are ineffective or impractical. The decision to use an approved fluoroquinolone in a food animal species, within a label claim, is a clinical decision rather than a regulatory one. The decision is made on the basis of the bacterial infection and its prevailing susceptibility, previous experience with other antimicrobials in a similar situation, and the clinical judgment of the veterinarian. Therefore, a greater responsibility must be placed on the veterinarian to balance the risk of antimicrobial resistance against the benefits anticipated from the use of specific antimicrobial agents. The task force cannot make regulatory recommendations. However, the task force recognizes that resolution of this issue of prudent use will impact on the regulatory decisions for fluoroquinolones and all future antimicrobials intended for approval for use in livestock and poultry. Therefore, because of the ban on the extralabel (for an indication not on the label) use of fluoroquinolones in food-producing animals (in the United States), the task force urges that the veterinary community continue use of fluoroquinolones only where indicated and approved.

If the animal agriculture community is to use the
model for a "prudent use" education campaign, similar to that directed by the CDC toward physicians and human patients, a strategic partnership must be forged that involves all stakeholders in the use of antimicrobials in food animals. Producers and their trade or breed associations, veterinarians, academicians, regulatory officials, and the pharmaceutical industry must unite to create and implement a comprehensive education program that can be immediately applied to clinical decision making at the veterinarian-animal level. This partnership will further promote food safety in general.

**What Constitutes Prudent Use of Antibacterials in Livestock and Poultry?**

The working definition of prudent use of an antimicrobial agent adopted by the task force is: use that provides the desired therapeutic effect (therapeutic as defined by the FDA-CVM to include treatment, control, and prevention of microbial diseases). We recognize a lack of data identifying which pattern of use minimizes the selection for resistant organisms in a clinical setting; therefore, the focus should be to maximize the therapeutic outcome.

Attempts to eradicate bacterial diseases completely from human and animal patients through comprehensive antimicrobial-use patterns are ill advised and doomed to failure. The prodigious number of bacteria, their rapid replication (and hence mutation rates), and promiscuous exchange of DNA offer several mechanisms to overcome the lethal action of virtually any antimicrobial. Consistent exposure to these agents offers selective pressure on emergence of existing resistant organisms. Therefore, use of antimicrobials must be geared to potent tactical strikes designed to control and prevent microbial diseases. We recognize one antimicrobial-use pattern is: use of an antimicrobial agent adopted by the task force is: use that provides the desired therapeutic effect (therapeutic as defined by the FDA-CVM to include treatment, control, and prevention of microbial diseases). We recognize a lack of data identifying which pattern of use minimizes the selection for resistant organisms in a clinical setting; therefore, the focus should be to maximize the therapeutic outcome.

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As long as necessary—Antimicrobials should be used for a long enough duration to attain maximum effect. Insufficient duration of administration can lead to recrudescence of the infection, with an increased likelihood for recrudescence by a strain that may be less susceptible, or even resistant, to the administered antimicrobial agent.

As short as possible—Limiting the duration of use to only that required for the therapeutic effect minimizes the exposure of the bacterial population to the antimicrobial. In turn, the adverse effects on the surviving commensal microflora are minimized and the medical impact of the remaining zoonotic organisms is minimized. Theoretically, antimicrobial use should be stopped as soon as the animal's own host defense (or immune) system can finish the job of controlling the pathogenic bacteria itself. This is an area of research need.

Education at the producer and veterinarian level is the key to prudent use of antimicrobials. These 2 groups must be committed to proper antimicrobial use, and both may benefit from forming even closer partnerships in this effort. Both groups must understand the importance of the selection for resistant populations of bacteria in their therapeutic decision making, not only because resistance is a public health issue, but also for maintenance of the drug's usefulness during an extended period in the target animal species.

These issues compel the veterinarian to become more familiar with the pharmacokinetics and pharmacodynamics of approved antibacterial agents, including those factors specific to the bacteria-drug-host-environment interactions that may enhance efficacy and reduce the selection of antimicrobial resistance among bacterial populations, or both. The veterinarian must be aware of the factors that should be considered (including bacterial and viral co-infections, and stress factors) in choosing the correct antimicrobial agent, especially dosage regimen and duration of therapy, and recognize that prudent use of antimicrobial agents is an important food safety consideration. The professional flexible labeling of prescription animal drugs provides an excellent mechanism to convey key information that can be used by the veterinarian to maximize the likelihood of efficacy in the individual patient, and about important characteristics of the antibacterial agent that affect efficacy, safety, tissue drug residues, and the potential for selection of antimicrobial resistance.

Two antimicrobial-use patterns that should be discouraged are the unwarranted and empirical rotation of antimicrobials, and the concurrent use of multiple antimicrobial products (when a known benefit is not detected) in the same animal population. The arbitrary rotation of antimicrobials in a food animal population in an attempt to reduce the development of bacterial resistance has not been proven to be an effective strategy. This suggests that arbitrary antimicrobial rotation may only serve to expose the bacterial population to a wider array of antimicrobials, thereby selecting for bacterial populations resistant to multiple antimicrobials.

Through increased educational campaigns, producers should become more convinced of the need for adequate diagnostics (including appropriate use of diagnostic laboratory resources as part of problem solving), treatment recommendations, and maintenance of medical records (including records regarding use of antimicrobials during an extended period). Furthermore, producers should become familiar with the medical importance of compliance with the prescribed dosage regimen and duration of therapy as well as the use of products for which efficacy has been established. Producers will more clearly appreciate the importance of discarding unused antimicrobials and of incorporating the veterinarian in all therapeutic decision making, including when to use over-the-counter antibacterial agents. Clearly written treatment directions within a valid veterinarian/client/patient relationship provide an excellent mechanism for communicating prudent drug use, and are required in the United States for any prescription drug use, including extralabel use of over-the-counter products.

Veterinarians and producers must be committed to prevention of infectious disease first. If poor husbandry and management are practiced, treatment interventions are costly and often ineffective. Treatment regimens are not a substitute for proper husbandry and management, both of which should foster disease prevention. Furthermore, improved understanding and identification of disease syndromes for which antimicrobials are not indicated will reduce unnecessary use of antimicrobials. Increased availability of economical, rapid, and accurate diagnostic resources for the producer and veterinarian, and increased surveillance and availability of bacterial susceptibility information for the animal species, farm, feedlot, local area, or region will enhance selection of effective antibacterial agents when they are warranted. Susceptibility information should be qualitative (ie, susceptible/intermediate/resistant) and quantitative (ie, minimum inhibitory concentrations of prevailing strains of bacteria). To emphasize the importance of bacterial susceptibility for food safety, this information should be incorporated into quality assurance programs. This will encourage livestock and poultry commodity groups to provide more widely available educational courses on livestock and poultry therapeutics and enlist the help of private veterinary practitioners.

Record keeping is a key component of prudent use. A commitment must be made between the producers and veterinarians to maintain accurate and detailed records of farm events, especially those concerning disease and the use of antimicrobial agents. Additionally, use of over-the-counter antimicrobials needs to be recorded and discussed with the veterinarian on a routine basis to ensure continued efficacy of the product. Antimicrobial use should be recorded along with therapeutic outcomes to monitor the efficacy of antimicrobial regimens used in production systems.

Research Needs

Finally, the task force also discussed research needs regarding antimicrobial resistance development.
Recommendations for future research are as follows:

- Conduct prospective epidemiologic (or controlled clinical) studies that better define antibacterial resistance sources.
- Develop a national (eventually international) surveillance system for monitoring the development and emergence of antimicrobial resistance in all clinically important bacterial pathogens in food-producing and companion animals.
- Evaluate natural emergence and selection for antimicrobial resistance.
- Define resistance mechanisms and develop in vivo models to test intervention strategies (eg, duration of treatment) designed to enhance prudent use.
- Define processes that reduce the persistence of resistant zoonotic organisms through the food chain (USDA Hazard Analysis and Critical Control Point programs and validation).
- Develop economical alternatives to the use of antimicrobials and evaluate the impact that alternatives (eg, vaccines, probiotics, competitive exclusion principles, nutrition, and new health technologies and strategies) might have on selection for resistance.
- Establish pharmacokinetic/pharmacodynamic relationships for approved and new drug classes.
- Conduct quantitative risk assessment of the [human] medical impact of use and nonuse of antibacterials in food animals for comparison with the risks associated with antibacterial use in human beings.
- Conduct risk analysis of economic, environmental, and social consequences attributable to use (and nonuse) of antimicrobials in food animals.
- Assess the epidemiology of transfer and the clonal dispersion of bacteria between animals and human beings in nonoutbreak or nonepidemic situations to evaluate the genetic similarity (and, hence, likelihood of transfer among bacterial species and from animals to human beings) of zoonotic bacteria.
- Standardize laboratory techniques and applicability of veterinary breakpoints.

The task force thanks all of the participants of the meeting for their presentations and discussions. Only through open dialogue and cooperation will we be able to minimize the risk of development of resistance to medically important antimicrobial agents.